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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/537,088	03/29/2000	Anil Kumar Dwivedi	82239	7351

7590 06/25/2002

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EXAMINER	
RUSSEL, JEFFREY E	

ART UNIT	PAPER NUMBER
1653	12

DATE MAILED: 06/25/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/537,088	DWIVEDI ET AL.	
	Examin r	Art Unit	
	Jeffrey E. Russel	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 May 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12,14 and 15* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12, 14, and 15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on May 3, 2002 has been entered.

2. The Sequence Listing filed May 3, 2002 has been approved.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

4. Claims 1, 2, 5-12, and 14 are rejected under 35 U.S.C. 103(a) as being obvious over the Nath et al article in view of Chiesi et al. The Nath et al article teaches the highly active opioid peptide L-Tyr-D-Ala-Gly-NMe-Phe-Gly-NHC_3H_7. The opioid peptide can be administered orally or i.p. See, e.g., the Abstract and page 269, column 1. The Nath et al article does not teach the opioid peptide in combination with a cyclodextrin derivative. Chiesi et al teach forming an inclusion complex of a basic drug and a cyclodextrin such as hydroxypropyl-β - cyclodextrin and dimethyl-β- cyclodextrin. The inclusion complex results in improved storage stability and enhanced water solubility and bioavailability for the drug. The drug is to be administered orally or parenterally. See, e.g., column 3, lines 15-21; column 8, lines 54-56; and claim 8. It would have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to combine the opioid peptide of the Nath et al article with the cyclodextrins of Chiesi et al in order to form inclusion complexes for pharmaceutical administration because the opioid peptide of the Nath et al article is a basic drug as required by Chiesi et al and because combining the opioid peptide of the Nath et al article with the cyclodextrins of Chiesi et al would

have been expected to increase the solubility and bioavailability of the opioid peptides, a result which is desirable for pharmaceutical agents. It would further have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to determine all operable and optimal ratios of opioid peptide and cyclodextrin derivative in the above-outlined compositions because component proportion is an art-recognized result-effective variable which is routinely determined and optimized in the pharmaceutical art.

5. Claims 1-3 and 7-11 are rejected under 35 U.S.C. 103(a) as being obvious over the European Patent Application '653 in view of the Nath et al article. The European Patent Application '653 teaches combining drugs, including peptide drugs such as enkephalins, with cyclodextrins, especially β-cyclodextrin. The combination permits the drugs to be administered nasally, thereby avoiding the problems of poor absorption after oral administration and avoiding undesirable metabolism of the drugs. See, e.g., column 1, lines 8-24; column 4, lines 4-11; and column 5, lines 31-36. The European Patent Application '653 does not teach administration of Applicants' particular opioid peptide. The Nath et al article teaches the highly active opioid peptide L-Tyr-D-Ala-Gly-NMe-Phe-Gly-NHC_3H_7. The opioid peptide can be administered orally or i.p. See, e.g., the Abstract and page 269, column 1. It would have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to administer the opioid peptide of the Nath et al article in the pharmaceutical formulations of the European Patent Application '653 because the opioid peptide of the Nath et al article is a specific known example of the peptide and enkephalin drugs which are contemplated by the European Patent Application '653 and because administering the opioid peptide of Nath et al nasally in the pharmaceutical formulations of the European Patent Application '653 would avoid problems of poor absorption

after oral administration and of undesirable metabolism as taught by the European Patent Application '653. It would further have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to determine all operable and optimal ratios of opioid peptide and β-cyclodextrin in the above-outlined compositions because component proportion is an art-recognized result-effective variable which is routinely determined and optimized in the pharmaceutical art.

6. Claims 1, 2, 4, 7-12, and 14 are rejected under 35 U.S.C. 103(a) as being obvious over Hora et al in view of the Nath et al article. Hora et al teach combining polypeptide drugs with cyclodextrins, β-cyclodextrin, including hydroxyethyl-β-cyclodextrin. The combination improves the solubility and the stability of polypeptide drugs, and permits oral administration as well. See, e.g., the Abstract; column 10, lines 31-45, column 11, lines 59-64; column 16, lines 30-32 and 43; column 18, lines 45-49; and column 26, line 66 - column 27, line 4. Hora et al do not teach administration of Applicants' particular opioid peptide. The Nath et al article teaches the highly active opioid peptide L-Tyr-D-Ala-Gly-NMe-Phe-Gly-NHC_3H_7. The opioid peptide can be administered orally or i.p. See, e.g., the Abstract and page 269, column 1. It would have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to administer the opioid peptide of the Nath et al article in the pharmaceutical formulations of Hora et al because the opioid peptide of the Nath et al article is a specific known example of the polypeptide drugs which are contemplated by Hora et al and because administering the opioid peptide of Nath et al in the pharmaceutical formulations of Hora et al would improve the solubility and the stability of the opioid peptide as taught by Hora et al. It would further have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to

determine all operable and optimal ratios of opioid peptide and -cyclodextrin in the above-outlined compositions because component proportion is an art-recognized result-effective variable which is routinely determined and optimized in the pharmaceutical art.

7. Claims 1, 7-12, and 15 are rejected under 35 U.S.C. 103(a) as being obvious over the French Patent '268 in view of the Nath et al article. The French Patent '268 teaches combining drugs, including analgesics and peptide hormones, with β-cyclodextrin. The combination permits the drugs to be administered transcutaneously. See the attached abstract. The French patent '268 does not teach administration of Applicants' particular opioid peptide. The Nath et al article teaches the highly active opioid peptide L-Tyr-D-Ala-Gly-NMe-Phe-Gly-NHC_3H_7. The opioid peptide can be administered orally or i.p. See, e.g., the Abstract and page 269, column 1. It would have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to administer the opioid peptide of the Nath et al article in the pharmaceutical formulations of the French Patent '268 because the opioid peptide of the Nath et al article is a specific known example of the analgesic drugs which are contemplated by the French Patent '268, because the French Patent '268 would have been expected to be useful in transcutaneously administering polypeptides such as the opioid peptide of the Nath et al article because of the French Patent '268's disclosed ability to administer polypeptide hormones, and because administering the opioid peptide of Nath et al transcutaneously in the pharmaceutical formulations of the French Patent '268 would avoid problems of poor absorption after oral administration or of intrusive i.p. administration methods. It would further have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to determine all operable and optimal ratios of opioid peptide and β-cyclodextrin in the above-outlined

compositions because component proportion is an art-recognized result-effective variable which is routinely determined and optimized in the pharmaceutical art.

8. Applicant's arguments filed May 3, 2002 have been fully considered but they are not persuasive.

Applicants contend that the compound of the Nath et al article does not include the N-methylphenylalanyl group required by Applicants' claims. The examiner disagrees. the "MePhe" group of the Nath et al article is synonymous with the "N-methylphenylalanyl" group required by Applicants' claims, both signifying that the amino group of a phenylalanine residue is substituted with a methyl group. The compound of the Nath et al article and the opioid peptide recited in Applicants' claims are the same compound.

Applicants contend that the "consisting essentially of" language present in the claims excludes the acid of Chiesi et al and the enhancer of absorption at a mucosal surface of the European Patent Application '653. However, "consisting essentially of" language excludes from Applicants' claims only those components which would materially affect the basic and novel characteristics of Applicants' claimed composition, with the burden being upon Applicants to make such a showing. See In re De Lajarte, 143 USPQ 256 (CCPA 1956) and MPEP 2111.03. Applicants have not submitted any evidence which would satisfy this burden.

Applicants contend that there is no motivation to combine the compound of the Nath et al article with the cyclodextrins of the other references because a person of ordinary skill in the art would recognize that the compound of the Nath et al article is already soluble in water and stable and therefore does not require improved water solubility or stability. However, Applicants have not provided any explanation as to why a person of ordinary skill in the art would recognize that

the compound of the Nath et al article is already soluble in water and stable. Further, unless a drug is perfectly water soluble and perfectly stable (and the examiner is not aware of any drug which matches either of these criteria), then there is always motivation in the art to improve water solubility and/or stability. Finally, Chiesi et al provide the additional motivation of improved bioavailability, the European Patent Application '653 provides the additional motivation of nasal administration, Hora et al provide the additional motivation of oral administration, and the French Patent '268 provides the additional motivation of transcutaneous administration. Any of these motivations is sufficient to support prima facie obviousness. Again, the motivation to establish prima facie obviousness need not be the same as Applicants'.

Applicants cite to the Uekema et al article as establishing that there is no reasonable expectation of success in forming orally available inclusion complexes containing the specific peptide of the invention. However, Applicants have not provided and made of record a copy of this article, and the article is not available in the Scientific and Technical Information Center, and accordingly the examiner can not rely upon the article to establish that there is no reasonable expectation of success. The examiner does note, however, that the date of the article as reported in Applicants' Remarks is 1994, and that whether or not there is a reasonable expectation of success must be established at the time Applicants' invention was made, i.e. in 2000. Because Chiesi et al, Hora et al, and the French Patent '268 were published after Uekema et al article and before Applicants' filing date, it is unlikely that the Uekema et al article can be relied upon to demonstrate that later developments in the art do not create a reasonable expectation of success in combining opioid peptides with cyclodextrins.

Applicants argue that a peptide:cyclodextrin ratio of 1:2 is more effective for oral delivery than a 1:1 ratio, whereas the reverse is true for transdermal delivery. However, Applicants have not provided evidence of this in appropriate form under 37 CFR 1.132, which is necessary in order to rely upon unexpected results to rebut a prima facie case of obviousness. Further, the rejected claims are not limited to peptide:cyclodextrin ratios of 1:2, and therefore the unexpected results discussed in Applicants' remarks are not commensurate in scope with Applicants' claims.

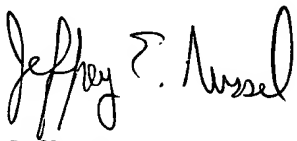
Express teachings are never necessary to support prima facie obviousness. See MPEP 2144, first full paragraph, first sentence. Further, Chiesi et al, the European Patent Application '653, Hora et al, and the French Patent '268 already establish a reasonable expectation of success that various drugs can be usefully combined with cyclodextrins, and therefore combination of the particular drug of the Nath et al article with cyclodextrins would reasonably have been expected to be successful for the purposes expressed in Chiesi et al, the European Patent Application '653, Hora et al, and the French Patent '268. Applicants have not indicated what parameters and possibilities would have to be tried until a successful combination was arrived at. The one parameter recited in Applicants' claims, i.e. opioid peptide:cyclodextrin molar ratio, is routinely determined and optimized by one skilled in the art. To date, Applicants have not supplied evidence that there are any critical parameters necessary to successfully combine an opioid peptide and a cyclodextrin. Unexpected results must be demonstrated, not alleged.

Applicants contend that their invention satisfies a long-felt need in the art. However, a long-felt need in the art must be demonstrated under 37 CFR 1.132. See MPEP 716.04 for the type of evidence needed to establish such secondary considerations of non-obviousness.

Again, the examiner emphasizes that the motivation to combine prior art references need not be the same as Applicants. See MPEP 2144 under "Rationale Different From Applicants' Is Permissible". Further, while Applicants' arguments stress that the claimed compositions have improved oral efficacy, Applicants' claims clearly contemplate non-oral administration of the compositions (see, e.g., the reference to injections in claim 10, and the reference to transdermal or rectal administration in claim 12). It is irrelevant that the prior art references do not teach or suggest oral administration where Applicants claims do not require oral administration. Applicants have not provided any evidence that the compositions disclosed by Chiesi et al, the European Patent Application '653, Hora et al, and the French Patent '268 are not orally efficacious. Note that the issue of whether or not prior art compositions are orally efficacious is different than the issue of whether or not prior art compositions are disclosed to be orally efficacious.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey E. Russel at telephone number (703) 308-3975. The examiner can normally be reached on Monday-Thursday from 8:30 A.M. to 6:00 P.M. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor Christopher Low can be reached at (703) 308-2923. The fax number for Art Unit 1653 for formal communications is (703) 305-3014; for informal communications such as proposed amendments, the fax number (703) 746-5175 can be used. The telephone number for the Technology Center 1 receptionist is (703) 308-0196.



Jeffrey E. Russel
Primary Patent Examiner
Art Unit 1653

JRussel
June 18, 2002